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Review

Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders

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ABSTRACT

Botulinum neurotoxin (BoNT) can be injected to achieve therapeutic benefit across a large range of clinical conditions. To assess the efficacy and safety of BoNT injections for the treatment of certain movement disorders, including blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, focal limb dystonias, laryngeal dystonia, tics, and essential tremor, an expert panel reviewed evidence from the published literature. Data sources included English-language studies identified via MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Central Register of Controlled Trials. Evidence tables generated in the 2008 Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (AAN) review of the use of BoNT for movement disorders were also reviewed and updated. The panel evaluated evidence at several levels, supporting BoNT as a class, the serotypes BoNT-A and BoNT-B, as well as the four individual commercially available formulations: abobotulinumtoxinA (A/Abo), onabotulinumtoxinA (A/Ona), incobotulinumtoxinA (A/Inco), and rimabotulinumtoxinB (B/Rima). The panel ultimately made recommendations for each therapeutic indication, based upon the strength of clinical evidence and following the AAN classification scale. For the treatment of blepharospasm, the evidence supported a Level A recommendation for BoNT-A, A/Inco, and A/Ona; a Level B recommendation for A/Abo; and a Level U recommendation for B/Rima. For hemifacial spasm, the evidence supported a Level B recommendation for BoNT-A and A/Ona, a Level C recommendation for A/Abo, and a Level U recommendation for A/Inco and B/Rima. For the treatment of oromandibular dystonia, the evidence supported a Level C recommendation for BoNT-A, A/Abo, and A/Ona, and a Level U recommendation for A/Inco and B/Rima. For the treatment of cervical dystonia, the published evidence supported a Level A recommendation for all four BoNT formulations. For limb dystonia, the available evidence supported a Level B recommendation for both

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A/Abo and A/Ona, but no published studies were identified for A/Inco or B/Rima, resulting in a Level U recommendation for these two formulations. For adductor laryngeal dystonia, evidence supported a Level C recommendation for the use of A/Ona, but a Level U recommendation was warranted for B/Rima, A/Abo, and A/Inco. For the treatment of focal tics, a Level U recommendation was warranted at this time for all four formulations. For the treatment of tremor, the published evidence supported a level B recommendation for A/Ona, but no published studies were identified for A/Abo, A/Inco, or B/Rima, warranting a Level U recommendation for these three formulations. Further research is needed to address evidence gaps and to evaluate BoNT formulations where currently there is insufficient or conflicting clinical data.

1. Introduction

The therapeutic use of botulinum neurotoxin (BoNT) has evolved from its initial application in the treatment of movement disorders, such as blepharospasm and other dystonias, to many other neurologic and non-neurologic disorders. This review will evaluate the evidence for the therapeutic application of BoNT to blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, focal limb dystonias, laryngeal dystonia, tics, and essential tremor.

In general, the therapeutic benefits of BoNT in movement disorders derive from its inhibitory actions on muscle contraction resulting from blockade of acetylcholine at the neuromuscular junction (Mayer and Esquenazi, 2003; Sheean, 2003). Accordingly, the primary effect of BoNT is relaxation of the affected skeletal muscle. However, considerable evidence suggests that BoNT injected peripherally may also influence central nervous system function (Gracies, 2004). By blocking gamma as well as alpha motor neurons, there is denervation of intrafusal muscle fibers (Giladi, 1997). This reduces muscle spindle afferent input to the central nervous system and thereby modifies sensorimotor and proprioceptive pathways (Giladi, 1997; Hallett, 2000; Rosales and Dressler, 2010). These mechanisms may contribute to the therapeutic effects of BoNT in focal dystonias beyond the effects anticipated on the basis of muscle relaxation alone.

1.1. Objectives

The aim of this review of evidence is to assess the effectiveness of BoNT injections for the treatment of movement disorders; the intent is to evaluate both the class- and formulation-specific effects of BoNT when the evidence allows. Two BoNT serotypes (A and B) are approved by the Food and Drug Administration (FDA) for clinical use in the United States. Approved BoNT-A formulations are onabotulinumtoxinA (A/Ona; Allergan, Inc.), abobotulinumtoxinA (A/Abo; Ipsen Limited), and incobotulinumtoxinA (A/Inco; Merz Pharmaceuticals); the only approved BoNT-B formulation is rimabotulinumtoxinB (B/Rima; Solstice Neurosciences, LLC). These agents are marketed under the brand names Botox®, Dysport®, Xeomin®, and Myobloc®/Neurobloc®, respectively.

2. Methods

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

All studies comparing BoNT injection or BoNT injection plus other pharmacologic and nonpharmacologic therapies to placebo, no treatment, or active comparators, or comparing doses, of BoNT were considered.

2.1.2. Types of subjects

Adults and children were included, as appropriate, based on each of the specific therapeutic indications of interest.

2.1.3. Types of interventions

Separate sections of the evidence tables were created for assessments of 1) effectiveness (placebo-controlled studies), 2) comparative effectiveness (active-controlled studies comparing different doses or formulations of BoNT or different pharmacologic therapies to BoNT), and 3) methodology, defined as studies comparing different modes of administration including location, type of imaging and other forms of guidance for injection, and nonpharmacologic treatments.

2.1.4. Types of outcome measures

From the studies reviewed, a variety of outcome measures were identified as potential measures of effectiveness for each disease/disorder of interest. Outcome measures could include variables related to body functions and body structures as well as patient- and/or investigator-reported outcomes such as health-related quality of life and perceived improvements. Generally placebo responses in these disorders are small or absent.

2.2. Search methods for identification of studies

The following terms were used to search several databases including MEDLINE, EMBASE, CINAHL, Current Contents, and the Cochrane Controlled Trials Register. Clinicaltrials.gov was also searched for additional studies that may not have been indexed in the former databases as of the cutoff data for inclusion (March 1, 2011). Only English-language articles were considered. Articles that were included were fully published (i.e., online and in print) or available as full text online in peer-reviewed